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INTELLECTUAL PROPERTY INDIA

GOVERNMENT OF INDIA
MINISTRY OF COMMERCE & INDUSTRY
PATENT OFFICE, DELHI BRANCH,
W - 5, WEST PATEL NAGAR,
NEW DELHI - 110 008.

REC'D 18 AUG 2003
WIPO PCT

I, the undersigned, being an officer duly authorized in accordance with the provision of the Patent Act, 1970 hereby certify that annexed hereto is the true copy of the ***Application, Provisional*** *and* ***Complete Specification*** *filed in connection with Application for Patent No.* ***616/Del/02*** *dated* ***7th June 2002.***

Witness my hand this 4th Day of July 2003.

(S.K. PANGASA)
Assistant Controller of Patents & Designs

PRIORITY DOCUMENT
SUBMITTED OR TRANSMITTED IN COMPLIANCE WITH RULE 17.1(a) OR (b)

0616 07 JUN 2002

Govt. of India Patent Office New Delhi Received Rs 5000 in cash. Cheque/M.O./D.D. 7/6/02 Vide Entry No. 293 in the Register of Valuables A. O ..... Cashier

FORM 1

THE PATENTS ACT, 1970
(39 of 1970)

APPLICATION FOR GRANT OF A PATENT

(See Sections 7, 54 and 135 and rule 33A)

1 We, **RANBAXY LABORATORIES LIMITED**, a Company incorporated under the Companies Act, 1956, Corporate Office at 19, Nehru Place, New Delhi - 110 019, India

2. hereby declare –

(a) that we are in possession of an invention titled **"A PROCESS OF MAKING SUSTAINED RELEASE PHARMACEUTICAL FORMULATIONS OF GABAPENTIN "**

(b) that the Provisional Specification relating to this invention is filed with this application.

(c) that there is no lawful ground of objection to the grant of a patent to us.

3. Further declare that the inventors for the said invention are

a. MANISH CHAWLA

b. RAJEEV S. RAGHUVANSHI

c. ASHOK RAMPAL

of Ranbaxy Laboratories Limited, Plot No. 20, Sector-18, Udyog Vihar Industrial Area, Gurgaon – 122001 (Haryana), India, all Indian Nationals.

4. That we are the assignee or legal representatives of the true and first inventors.

5. That our address for service in India is as follows:

DR. B. VIJAYARAGHAVAN
Associate Director – Intellectual Property
Ranbaxy Laboratories Limited
Plot No.20, Sector – 18,
Udyog Vihar Industrial Area,
Gurgaon – 122001 (Haryana), INDIA.
Tel. No. (91-124) 6343126; 6342001 – 10; 8912501-10
Fax No. (91-124) 6342027

ORIGINAL

6. Following declaration was [redacted]n by the inventors in the convention co[redacted]:

We, MANISH CHAWLA, RAJEEV S. RAGHUVANSHI, ASHOK RAMPAL of Ranbaxy Laboratories Limited, Plot No. 20, Sector – 18, Udyog Vihar Industrial Area, Gurgaon–122001 (Haryana), India, all Indian Nationals, the true and first inventors for this invention in the convention country declare that the applicants herein, **Ranbaxy Laboratories Limited**, 19, Nehru Place, New Delhi - 110 019, India, is our assignee or legal representative.

a.

(MANISH CHAWLA)

b.

(RAJEEV S. RAGHUVANSHI)

c.

(ASHOK RAMPAL)

7. That to the best of our knowledge, information and belief the fact and matters stated herein are correct and that there is no lawful ground of objection to the grant of patent to us on this application.

8. Followings are the attachment with the application:

   a. Provisional Specification (3 copies)
   b. Drawings (3 copies)
   c. Statement and Undertaking on FORM – 3
   d. Fee Rs.5,000/- (Rupees Five Thousand only..) in cheque bearing No. **682449** dated **05.06.2002** on **ANZ Grindlays Bank, New Delhi.**

We request that a patent may be granted to us for the said invention.

Dated this 7TH day of **JUNE, 2002**.

For Ranbaxy Laboratories Limited

(SUSHIL KUMAR PATAWARI)
COMPANY SECRETARY

FORM 2

The Patents Act, 1970
(39 of 1970)

PROVISIONAL SPECIFICATION
(See Section 10)

A PROCESS OF MAKING SUSTAINED RELEASE PHARMACEUTICAL FORMULATIONS OF GABAPENTIN

RANBAXY LABORATORIES LIMITED
19, NEHRU PLACE, NEW DELHI - 110019
(A Company incorporated under the Companies Act, 1956)

The following specification particularly describes and ascertains the nature of this invention and the manner in which it is to be performed:

The present invention relates to a process of making sustained release pharmaceutical formulations of Gabapentin.

Gabapentin is indicated as an adjunctive therapy in the treatment of partial seizures with and without secondary generalization in adults with epilepsy. Gabapentin has also been approved for neuropathic pain in some of the countries.

Some epileptic patients need to take medication throughout their lives while others may only require it for a limited period. The importance of taking drugs at regular intervals cannot be overemphasized. However, it is not easy for everyone to remember to take the correct dose at the same time each day. Multiple dosing is not only inconvenient it also lowers patient compliance.

Gabapentin has a relatively short half-life, which leads to substantial fluctuations in the plasma concentration of the drug. Frequent dosing is necessary to maintain reasonably stable plasma concentrations. Gabapentin conventional dosage forms like tablet, or capsule are administered three times a day. This mode of therapy leads to high drug concentration in the blood after dosing, and then a rapid decrease in drug concentrations as a result of drug distribution, metabolism and elimination. The concentration difference in C_{max} & C_{min} is a major disadvantage associated with conventional dosage forms.

Patient non-adherence to antiepileptic therapy is the most important cause of poor control and for the development of status epilepticus. Moreover, patient compliance in epilepsy is compromised owing to long duration of therapy. Therefore, need exists for a dosage form that increases patient compliance by providing a dosage form that requires fewer doses.

The primary object of this invention is to provide a twice a day dosage form of gabapentin.

Another object of the invention is to provide a dosage form of gabapentin, which provides gabapentin blood level in a therapeutic range over an extended time period.

Another object of the present invention is to provide a sustained-release dosage form of gabapentin that minimizes drug plasma fluctuations.

According to the present invention gabapentin twice a day formulation comprises gabapentin in admixture with a sufficient quantity of at least one pharmaceutically acceptable polymer.

The pharmaceutically acceptable polymer is a water-soluble/insoluble hydrophilic polymer, or a water insoluble hydrophobic polymer (including waxes).

Examples of suitable water soluble polymers include polyvinylpyrrolidone, hydroxypropyl cellulose, hydroxypropyl methyl cellulose, methyl cellulose, vinyl acetate copolymers, polysaccharides (such as alignate, xanthum gum, etc.) polyethylene oxide, methacrylic acid copolymers, maleic anhydride/methyl vinyl ether copolymers and derivatives and mixtures thereof.

Examples of suitable water insoluble hydrophobic polymers include acrylates, cellulose derivatives such as ethylcellulose or cellulose acetate, polyethylene, methacrylates, acrylic acid copolymers and high molecular weight polyvinylalcohols. Examples of suitable waxes include fatty acids and glycerides.

The amount of the polymer in the dosage form may vary from about 5% to about 80% by weight of the composition.

Invention may further contain other additives or excipients such as diluents, lubricants, binders, stabilizers etc.

Suitable diluents include powdered sugar, calcium phosphate, calcium sulfate, microcrystalline cellulose, lactose, mannitol, kaolin, sodium chloride, dry starch, sorbitol, etc.

Examples of suitable lubricants include talc, stearic acid, vegetable oil, calcium stearate, zinc stearate, magnesium stearate, etc.

Examples of suitable glidants include talc, silicon dioxide, and cornstarch.

Examples of suitable binders include polyvinylpyrrolidone, xanthan gum, cellulose gums such as carboxymethylcellulose, methylcellulose, hydroxypropyl methylcellulose, hydroxypropyl cellulose, gelatin, starch, pregelatinized starch etc.

Examples of suitable stabilizers include hydroxypropyl methylcellulose, poloxamers etc.

Other excipients that may be incorporated into the formulation include preservatives, antioxidants, or any other excipient commonly used in the pharmaceutical industry, etc.

The matrix formulations are generally prepared using standard techniques well known in the art. The tablets of the present invention may be prepared by dry blending gabapentin with controlled release polymer; wet granulating the blend with water or aqueous solution of binder; drying and sizing the wet granules; and compressing the granules.

Alternatively, non-aqueous granulation, direct compression or dry granulation techniques may also be used to prepare tablets.

The compositions of the invention can be administered orally in the form of tablets, pills or granulate filled into capsules.

Tablets and pills can additionally be prepared with enteric coatings and other release-controlling coatings.

The invention is further illustrated by the following examples but they should not be construed as limiting the scope of the invention anyway.

TABLE 1- Examples 1-3

Ingredients	Formulation 1	Formulation 2	Formulation 3
Gabapentin	900 mg	900 mg	900 mg
HPMC-low molecular weight	127.5 mg	100 mg	127.5 mg
HPMC-high molecular weight	125 mg	-	-
Microcrystalline cellulose	72.5 mg	110 mg	197.5 mg
Magnesium Stearate	7.5 mg	7.5 mg	7.5 mg
Colloidal Silicon Dioxide	7.5 mg	7.5 mg	7.5 mg
Total weight	1240 mg	1125 mg	1240 mg

Table 2: Drug release profile of tablets prepared as per the composition of Examples 1-3. (in USP2 apparatus at 50 RPM in 0.06N HCl; 900 ml)

Time (hr)	Formulation 1	Formulation 2	Formulation 3
0.5	-	18	17
1	24	29	27
2	35	49	43
4	56	72	68
6	71	97	83
8	83	-	96
10	98	-	101
12	104	-	-

Dated this 7TH day of **June, 2002.**

For Ranbaxy Laboratories Limited

(Sushil Kumar Patawari)
Company Secretary

FORM 2

The Patents Act, 1970
(39 of 1970)

27 MAY 2003

COMPLETE SPECIFICATION
(See Section 10)

SUSTAINED RELEASE ORAL DOSAGE FORMS OF GABAPENTIN AND A PROCESS FOR THE PREPARATION THEREOF

RANBAXY LABORATORIES LIMITED
19, NEHRU PLACE, NEW DELHI - 110019
(A Company incorporated under the Companies Act, 1956)

The following specification particularly describes and ascertains the nature of this invention and the manner in which it is to be performed:

The present invention relates to sustained release oral dosage forms of gabapentin and a process for the preparation thereof.

Gabapentin (1-(aminomethyl)cyclohexaneacetic acid) is an γ-amino acid analogue effective in the treatment of epilepsy. Gabapentin is indicated as an adjunctive therapy in the treatment of partial seizures with and without secondary generalization in adults with epilepsy. Gabapentin has also been approved for neuropathic pain in some of the countries.

Some epileptic patients need to take medication throughout their lives while others may only require it for a limited period. The importance of taking drugs at regular intervals cannot be overemphasized. However, it is not easy for everyone to remember to take the correct dose at the same time each day. Multiple dosing is not only inconvenient but also lowers patient compliance.

Gabapentin has a relatively short half-life (5-7hours), which leads to substantial fluctuations in the plasma concentration of the drug. Frequent dosing is necessary to maintain reasonably stable plasma concentrations. The effective dose of gabapentin is 900 to 1800 mg/day, which is given, in divided doses. Gabapentin conventional dosage forms like tablets or capsules are administered three times a day. This mode of therapy leads to sudden high drug concentration in the blood after dosing, and then a rapid decrease in drug concentrations as a result of drug distribution, metabolism and elimination. The high difference in minimum and maximum plasma concentration is a major disadvantage associated with conventional dosage forms. A sustained release dosage form of gabapentin would solve these shortcomings of conventional dosage forms. Gabapentin in such a form can be designed to give in one or two daily doses, thus requiring less frequent dosing and improving patient compliance. Effective plasma levels can be maintained within the therapeutic range with minimum of fluctuations in blood levels of gabapentin in comparison to conventional dosage forms. The steady plasma levels will reduce side effects and increase the therapeutic efficacy.

It has been found that gabapentin is typically absorbed from the upper intestine i.e. it has a narrow absorption window and is absorbed by active transport through a large neutral amino acid (LNAA) transporter. This transporter is located in upper small intestine and

has limited transport capacity and becomes saturated at high drug concentrations. Consequently, the plasma levels of gabapentin are not dose proportional and therefore, higher doses do not give proportionately higher plasma levels. Since the LNAA transporter responsible for gabapentin absorption is present specifically in the upper region of the intestine, the dosage form should be designed to release gabapentin in the stomach at a rate such that maximum drug is available in the intestinal segment. Conventional dosage forms release most of gabapentin in the stomach within a short time and consequently there are chances of drug being incompletely absorbed from the upper region of the intestine.

The sustained release dosage forms are designed to release drugs over an extended period of time and usually throughout the GI tract. Under these circumstances, drugs having a narrow absorption window tend to show poor absorption since a sustained release dosage form comprising such a drug is most likely to pass beyond the specific absorption site containing a substantial portion of the drug. This may lead to sub-therapeutic blood levels of the drug and quick termination of drug action and hence ineffective treatment.

US Patent No. 5,955,103 discloses an osmotic dosage form for sustained release of antiepileptic drugs. The dosage form comprises an outer wall and an inner membrane in contact with the outer wall. Inside the dosage form, there are two layers, the drug layer in contact with an expandable polymeric layer. There is an exit orifice in the wall and membrane from which the drug release takes place. The outer wall maintains the integrity of the dosage form and protects the inner membrane and the enclosed layers from the variable pH environment of the gastrointestinal tract (GI). Once inside the stomach, water penetrates the dosage form and the expandable polymeric layer absorbs water and swells thereby pushing the drug out through the orifice to the outside of the dosage form.

The process to formulate such osmotic dosage forms requires many steps of manufacturing and is expensive. There exists a lag time before drug release takes place from these dosage forms. Also, there are chances of dose dumping in case the dosage form ruptures in contact with food in the gastro-intestinal tract. Sustained release dosage

form of gabapentin, which [redacted]mple to prepare and is able to ma[redacted]n effective plasma concentration over an extended period of time would be desirable.

Considering the fact that gabapentin has narrow absorption window, a sustained release dosage form is desirable which can give increased exposure of gabapentin to LNAA transporter over an extended time period for efficient absorption. In order to achieve such an objective, the dosage form with a sustained release mode can be designed to have relatively extended gastric residence time in the stomach where the slow release of gabapentin can take place. The controlled amount of gabapentin will pass from the stomach to the upper intestine and become available for absorption. This will ensure that LNAA transporter does not become saturated thereby achieving maximal absorption of the drug.

We have now discovered that sustained release tablets of the invention could provide therapeutic levels of gabapentin with reduced number of administered doses. The rate and extent of absorption form sustained release tablets according to the invention given twice a day is same in comparison to a conventional tablet given three times a day for similar cumulative daily dose. These sustained release tablets maintain gabapentin plasma levels in a therapeutic range over an extended time period. A process for preparing the same is also provided which is less time-consuming, can be easily carried out and is economical.

Therefore, in one general aspect it relates to a sustained release tablet comprising gabapentin or a pharmaceutically acceptable salt or hydrates thereof and at least one rate-controlling polymer wherein the tablet provides therapeutically effective plasma levels of gabapentin for a period of up to about 12 hours.

In another general aspect it relates to a sustained release tablet comprising gabapentin or a pharmaceutically acceptable salt or hydrates thereof and at least one water-swellable cellulosic polymer wherein the tablet provides therapeutically effective plasma levels of gabapentin for a period of up to about 12 hours.

In another general aspect it relates to a sustained release tablet comprising gabapentin or a pharmaceutically acceptable salt or hydrates thereof and hydroxypropyl

methylcellulose wherein the tablet provides therapeutically effective plasma levels of gabapentin for a period of up to about 12 hours.

In another general aspect it relates to a sustained release tablet comprising gabapentin or a pharmaceutically acceptable salt or hydrates thereof and hydroxypropylcellulose wherein the tablet provides therapeutically effective plasma levels of gabapentin for a period of up to about 12 hours.

In another general aspect it relates to a sustained release tablet comprising gabapentin or a pharmaceutically acceptable salt or hydrates thereof, hydroxypropylmethylcellulose and hydroxypropylcellulose wherein the tablet provides therapeutically effective plasma levels of gabapentin for a period of up to about 12 hours.

In another general aspect it relates to a sustained release tablet comprising gabapentin or a pharmaceutically acceptable salt or hydrates thereof and at least one rate-controlling polymer; so that said tablet exhibits the following in-vitro dissolution profile, when measured in a USP type II dissolution apparatus, at 50 rpm, at a temperature of 37±0.5°C in 900ml of 0.06N hydrochloric acid;

- at most about 50% of the drug is released in 1 hour;
- at most about 65% of the drug is released in 2 hours and
- at most about 85% of the drug is released in 4 hours.

In another general aspect it relates to a sustained release tablet comprising gabapentin or a pharmaceutically acceptable salt or hydrates thereof and at least one rate-controlling polymer wherein the tablet given twice a day is comparable in bioavailability to the conventional Neurontin® commercially available gabapentin tablet/capsule of Pfizer given thrice-a-day under fasting conditions for same cumulative daily dose.

In one general aspect it relates to a sustained release tablet comprising gabapentin or a pharmaceutically acceptable salt or hydrates thereof and at least one rate-controlling polymer wherein the tablet has relatively extended gastric residence time and the tablet provides for the sustained release of gabapentin in the stomach environment over a prolonged period of time.

In another general aspect it relates to a process for the preparation of a sustained release tablet comprising granulating a mixture comprising gabapentin or a pharmaceutically acceptable salt or hydrates thereof and at least one rate-controlling polymer and optionally other excipients; compressing the granules into a tablet wherein the tablet provides therapeutically effective plasma levels of gabapentin for a period of up to about 12 hours.

In another general aspect it relates to a process for the preparation of a sustained release tablet comprising granulating a mixture comprising gabapentin or a pharmaceutically acceptable salt or hydrates thereof and at least one water-swellable cellulosic polymer; compressing the granules into a tablet wherein the tablet provides therapeutically effective plasma levels of gabapentin for a period of up to about 12 hours.

In another general aspect it relates to a process for the preparation of a sustained release tablet comprising granulating a mixture comprising gabapentin or a pharmaceutically acceptable salt or hydrates thereof and hydroxypropyl methylcellulose; compressing the granules into a tablet wherein the tablet provides therapeutically effective plasma levels of gabapentin for a period of up to about 12 hours.

In another general aspect it relates to a process for the preparation of a sustained release tablet comprising granulating a mixture comprising gabapentin or a pharmaceutically acceptable salt or hydrates thereof and hydroxypropylcellulose; compressing the granules into a tablet wherein the tablet provides therapeutically effective plasma levels of gabapentin for a period of up to about 12 hours.

In another general aspect it relates to a process for the preparation of a sustained release tablet comprising granulating a mixture comprising gabapentin or a pharmaceutically acceptable salt or hydrates thereof, hydroxypropylmethylcellulose and hydroxypropylcellulose; compressing the granules into a tablet wherein the tablet provides therapeutically effective plasma levels of gabapentin for a period of up to about 12 hours.

In another general aspect it relates to a process for the preparation of a sustained release tablet comprising granulating a mixture comprising gabapentin or a pharmaceutically acceptable salt or hydrates thereof and at least one rate-controlling polymer; compressing the granules into a tablet so that said tablet exhibits the following in-vitro dissolution profile, when measured in a USP type II dissolution apparatus, at 50 rpm, at a temperature of 37±0.5°C in 900ml of 0.06N hydrochloric acid;

- at most about 50% of the drug is released in 1 hour;
- at most about 65% of the drug is released in 2 hours and
- at most about 85% of the drug is released in 4 hours.

In another general aspect it relates to a process for the preparation of a sustained release tablet comprising granulating a mixture comprising gabapentin or a pharmaceutically acceptable salt or hydrates thereof and at least one rate-controlling polymer wherein the tablet given twice a day is comparable in bioavailability to a conventional Neurontin® commercially available gabapentin tablet/capsule of Pfizer given thrice-a-day under fasting conditions for similar cumulative daily dose.

In another general aspect it relates to a process for the preparation of a sustained release tablet comprising granulating a mixture comprising gabapentin or a pharmaceutically acceptable salt or hydrates thereof and at least one rate-controlling polymer; compressing the granules into a tablet wherein the tablet has relatively extended gastric residence time and the tablet provides for the sustained release of gabapentin in the stomach environment over a prolonged period of time.

Gabapentin is a highly water-soluble drug having a solubility of about 1 part in 20 parts of water. The sustained release of gabapentin, which has such a high solubility, is provided by formulating a tablet comprising dispersing gabapentin in a swellable polymeric matrix. In the presence of gastric fluids, the matrix swells by imbibing water and slowly releases the incorporated gabapentin by a combination of both diffusion and erosion. There is diffusion of the drug from the swollen matrix to the surrounding fluids owing to a concentration gradient of the drug between the swollen matrix and gastric fluid. Also, in the swollen state, the polymeric matrix slowly dissolves from the surface and releases the drug. The tablet in swollen state may retain its shape for sufficiently long time.

The sustained release dosage form described herein may be prepared by blending gabapentin with at least one rate-controlling polymer and other excipients; wet granulating the blend with water or a binder solution; drying and sizing the wet granules; and compressing the granules into tablets.

Gabapentin may be present as a free base, hydrated form such as monohydrate or any other pharmaceutically acceptable salt thereof with the anion of the mineral acid (calculated as chloride content) being less than 100 ppm and lactam content being less than 0.05% weight by weight of gabapentin. Gabapentin may comprise from about 100mg to about 1200 mg by weight of the tablet.

The rate-controlling polymer may be a either hydrophilic or hydrophobic polymer; particularly suitable are polymers that swell in aqueous media. The amount of polymer in the tablet relative to gabapentin depends upon the rate of drug release required and also upon the type and molecular weight of the polymer and other excipients present in the formulation. Examples of suitable rate-controlling polymers include polyvinylpyrrolidone; cellulosic polymers such as hydroxypropyl methylcellulose, hydroxypropylcellulose, hydroxyethylcellulose, methylcellulose; vinylacetate copolymers; polysaccharides (such as alginate, xanthan gum, guar gum etc.), starch and starch based polymers, polyethylene oxide, methacrylic acid copolymers, maleic anhydride/methyl vinyl ether copolymers and derivatives and mixtures thereof. Particularly suitable are hydroxypropyl methylcellulose and hydroxypropylcellulose. Hydroxypropyl methylcellulose can be of different viscosity grades having viscosity from about 100 cps to about 100,000 cps. Suitable types are sold under the trade name Methocel by Dow Chemical Co. such as Methocel K4MCR, Methocel K15MCR and Methocel K100MCR. Hydroxypropylcellulose can also be of different viscosity grades such as sold by Aqualon under the brand name of Klucel and also by Nippon Soda Co. Ltd, Japan. Suitable grades are those having viscosity of from about 7 to about 30,000 cps. Especially suitable among these hydroxypropylcelluloses are those having viscosity of 4000 to about 30,000 cps. Besides the above, cellulose derivatives such as ethylcellulose or cellulose acetate, methacrylates, acrylic acid polymers and copolymers, high molecular weight polyvinylalcohols and waxes such as fatty acids and glycerides are also included. The amount of the polymer in the dosage form may vary from about 5% to about 80% by

weight of the composition, in particular from about 5 to about 70%, more particularly from about 5 to 60% by weight of the composition.

The sustained release gabapentin tablets as described herein may further comprise other additives or excipients such as diluents, lubricants, binders, stabilizers etc. Suitable diluents include powdered sugar, calcium phosphate, calcium sulfate, microcrystalline cellulose, lactose, mannitol, kaolin, dry starch, sorbitol, etc. Lubricants can be talc, stearic acid, vegetable oil, calcium stearate, zinc stearate and magnesium stearate and glidants include talc, silicon dioxide and cornstarch. The binders include polyvinylpyrrolidone, polyvinylpyrrolidone/vinyl acetate copolymer; xanthan gum, guar gum; cellulose ethers such as carboxymethylcellulose, methylcellulose, hydroxypropyl methylcellulose, hydroxypropyl cellulose; gelatin, starch and its derivatives. The stabilizer may be poloxamer.

Gabapentin sustained release tablets may be prepared using the following steps:

1. Gabapentin is blended with rate-controlling polymer(s) and optionally with other excipients in a suitable mixer.
2. The blend of step 1 is granulated with water or a binder solution.
3. Granules are dried and sized.
4. Sized granules are mixed with other excipients such as stabilizer, lubricant, glidant and compressed into a tablet.

Alternatively, non-aqueous granulation, direct compression or dry granulation techniques may also be used to prepare tablets. In direct compression the blend of gabapentin, rate-controlling polymer(s), diluent, binder, stabilizer, lubricant is prepared and compressed into a tablet. The dry granulation process can be carried out by compaction or by preparing slugs of a mixture of gabapentin, rate-controlling polymer(s) and optionally other excipients; sizing of the material/slugs so obtained and mixing with a lubricant and compressing into a tablet.

Tablets can additionally be coated with non-rate-controlling polymer(s) compositions like Opadry® sold by Colorcon to impart aesthetic appeal. Such a coating may comprise about 2% by weight of the tablet.

Gabapentin sustained release tablet and process for the preparation thereof described herein is further illustrated by the following examples but these should not be construed as limiting the scope of the invention.

Ingredients	Quantity (mg)						
	Example 1	Example 2	Example 3	Example 4	Example 5	Example 6	Example 7
Gabapentin	900	900	900	900	900	600	450
Hydroxypropylmethyl cellulose	100	250	100	----	-----	100	75
Hydroxypropylcellulose	----	----	----	120	265		
Microcrystalline cellulose	110	----	----	-----	-----		
Mannitol	----	76	81	60.5	15.5	37	27.75
Polyvinylpyrrolidone/vinyl acetate copolymer	----	12	12	12	12	8	6
Poloxamer 407	----	12	12	15	15	10	7.5
Magnesium Stearate	7.5	15	15	20	20	10	7.5
Colloidal Silicon Dioxide	7.5	----	----	----	----		
Talc	----	15	15	22.5	22.5	10	7.5
Total weight	**1125**	**1280**	**1135**	**1150**	**1250**	**775**	**581.25**

Method:

Example 1

Gabapentin was mixed with a portion of hydroxypropylmethylcellulose, microcrystalline cellulose in a rapid mixer granulator and granulated with the aqueous solution of the remaining portion of hydroxypropylmethylcellulose. The wet mass was dried and suitably sized, lubricated with magnesium stearate, colloidal silicon dioxide and compressed with appropriate tooling. The tablets were subsequently coated with OPADRY to a weight build up of about 2% w/w.

Examples 2 and 3

Gabapentin was mixed with mannitol and a portion of hydroxypropylmethyl cellulose in a rapid mixer granulator and granulated with an aqueous solution/dispersion of polyvinylpyrrolidone/vinyl acetate copolymer and remaining portion of hydroxypropyl methylcellulose. The wet mass was dried and suitably sized, mixed with poloxamer, magnesium stearate, and talc and compressed with appropriate tooling. The tablets were subsequently coated with OPADRY to a weight build up of about 2% w/w.

Examples 4 and 5

Gabapentin was mixed with a portion of hydroxypropylcellulose and mannitol in a rapid mixer granulator, and granulated with an aqueous solution/dispersion of a portion of hydroxypropylcellulose. The wet mass was dried and suitably sized, mixed with remaining excipients and compressed with appropriate tooling. The tablets were subsequently coated with OPADRY to a weight buildup of about 2% w/w.

Examples 6 and 7

Gabapentin was mixed with a portion of hydroxypropylmethylcellulose and mannitol in a rapid mixer granulator and granulated with the aqueous solution/dispersion of a portion of hydroxypropylmethylcellulose. The wet mass was dried, suitably sized, blended with remaining excipients and compressed with appropriate tooling. The tablets were subsequently coated with OPADRY to a weight build up of about 2% w/w.

Tablets of Examples 1-7 were subjected to dissolution studies in a USP II apparatus in 0.06N HCl (900ml). The temperature and agitation were set at 37 °C ± 0.5 °C and 50rpm, respectively. Aliquot of sample was withdrawn at predetermined time intervals

and replaced with an equal amount of fresh media. Samples were processed and analyzed suitably. Dissolution profiles of these tablets are given in Table 1.

Table 1: Dissolution profile of tablets prepared as per the compositions of examples 1-7.

Time (hr)	% Drug release						
	Example 1	Example 2	Example 3	Example 4	Example 5	Example 6	Example 7
0.5	16	--	16	18	--	16	18
1	26	21	29	29	24	26	29
2	43	33	50	47	36	42	47
4	70	51	78	75	52	69	74
6	89	66	95	95	65	85	91
8	99	78	100	104	77	95	98
10	--	86	--		87		
12	--	92	--		93		

The tablets of examples 1, 3, 4, 6 and 7 released almost the entire drug within 8 hours, while tablets of examples 2 and 5 released about 90% of drug in 12 hours.

Bioavailability study:

The sustained release tablets of Example 1(test) were subjected to a bioavailability study in comparison with an immediate release formulation (NEURONTIN® 600mg as reference) in an open label, randomized, 2-way cross over study in 12 healthy male volunteers under fasting conditions. NEURONTIN® 600mg was given thrice a day every 8 hours and tablets prepared as per example 1 were given twice a day at 12 hours interval. Plasma C_{max} of Reference and Test products in individual human subjects are given in Table 2. The mean C_{max} and mean AUC_{0-24} of test and reference in the 12 human subjects is given in Table 3. The mean AUC_{0-24} and C_{max} of test was comparable to that of reference at the end of 24 hours.

Table 2: **Plasma C_{max} of Reference product given thrice a day and Test product given twice a day in human subjects.**

Subject	C_{max} (µg/mL)	
	Reference (Neurontin)	Test (example 1)
1	18.69	23.79
2	13.02	14.52
3	10.25	6.22
4	9.39	10.92
5	27.08	23.75
6	19.27	14.10
7	7.79	19.35
8	11.84	12.29
9	19.71	25.97
10	13.65	9.19
11	16.26	19.02
12	17.81	14.92

Table 3: **Mean C_{max} and AUC_{0-24} of Test and Reference products in human subjects**

	C_{max} (µg/mL)	AUC_{0-24} (µg.h/mL)
Test (Example 1)	16.17	199.32
Neurontin® 600 mg (Reference)	15.40	199.57

We claim:

1. A process for the preparation of a sustained release tablet comprising granulating a mixture comprising gabapentin or a pharmaceutically acceptable salt or hydrates thereof; at least one rate-controlling polymer and optionally other excipients with water or binder solution; compressing the granules into a tablet wherein the tablet provides therapeutically effective plasma levels of gabapentin for a period of upto about 12 hours.

2. The process according to claim 1 wherein the tablet exhibits the following in-vitro dissolution profile, when measured in a USP type II dissolution apparatus, at 50 rpm, at a temperature of 37±0.5°C in 900ml of 0.06N hydrochloric acid;

- at most about 50% of the drug is released in 1 hour;
- at most about 65% of the drug is released in 2 hours and
- at most about 85% of the drug is released in 4 hours.

3. The process according to claim 1 wherein the tablet given twice a day is comparable in bioavailability to conventional Neurontin® tablet/capsule given thrice a day under fasting conditions for similar cumulative daily dose.

4. The process according to claim 1 wherein the rate-controlling polymer comprises from about 5% to about 80% by weight of the tablet.

5. The process according to claim 4 wherein the rate-controlling polymer comprises from about 5% to about 70% by weight of the tablet.

6. The process according to claim 5 wherein the rate-controlling polymer comprises from about 5% to about 60% by weight of the tablet.

7. The process according to claim 1 wherein the rate-controlling polymer comprises polyvinylpyrrolidone; cellulosic polymer; vinylacetate copolymers; alginate, xanthan gum, guar gum; starch and starch based polymers, polyethylene oxide,

methacrylic acid copoly[redacted]s, maleic anhydride/methyl vinyl et[redacted]copolymers and derivatives, ethyl cellulose, cellulose acetate, methacrylates, acrylic acid polymers and copolymers, high molecular weight polyvinyl alcohols, waxes and combinations thereof.

8. The process according to claim 7 wherein the rate-controlling polymer is a cellulosic polymer.

9. The process according to claim 8 wherein the cellulosic polymer is selected from hydroxypropyl methylcellulose, hydroxypropylcellulose, hydroxyethylcellulose, methylcellulose and combination thereof.

10. The process according to claim 9 wherein the cellulosic polymer is hydroxypropyl methylcellulose.

11. The process according to claim 10 wherein hydroxypropyl methylcellulose has viscosity of about 100 cps to about 100,000 cps.

12. The process according to claim 11 wherein hydroxypropyl methylcellulose has viscosity of about 15,000 cps.

13. The process according to claim 11 wherein hydroxypropyl methylcellulose has viscosity of about 4000 cps.

14. The process according to claim 9 wherein the cellulosic polymer is hydroxypropylcellulose.

15. The process according to claim 14 wherein the hydroxypropylcellulose has viscosity of about 7 cps to about 30,000 cps.

16. The process according to claim 15 wherein the hydroxypropylcellulose has viscosity of about 4000 cps.

17. The process according to claim 15 wherein the hydroxypropylcellulose has viscosity of about 15000 cps.

18. The process according to claim 9 wherein the cellulosic polymer is hydroxyethylcellulose.

19. The process according to claim 1 wherein the other excipients comprise diluents, lubricants, glidant, binders, stabilizers and like.

20. The process according to claim 19 wherein diluent is selected from powdered sugar, calcium phosphate, calcium sulfate, microcrystalline cellulose, lactose, mannitol, kaolin, dry starch, sorbitol, and combinations thereof.

21. The process according to claim 19 wherein lubricant is selected from talc, stearic acid, vegetable oil, calcium stearate, zinc stearate, magnesium stearate, and combinations thereof.

22. The process according to claim 19 wherein the glidant is selected from talc, silicon dioxide, cornstarch and combinations thereof.

23. The process according to claim 19 wherein the binder is selected from polyvinylpyrrolidone, polyvinylpyrrolidone/vinylacetate copolymer, xanthan gum, guar gum, cellulose gums such as carboxymethylcellulose, methylcellulose, hydroxypropyl methylcellulose, hydroxypropyl cellulose, gelatin, starch, pregelatinized starch and combinations thereof.

24. The process according to claim 19 wherein the stabilizer is poloxamer.

25. A process according to claim 1 wherein sustained release tablet of gabapentin comprises granulating a mixture of a therapeutically effective amount of gabapentin or a pharmaceutically acceptable salt or hydrate thereof; about 5% to about 80% of rate controlling polymer i.e. hydroxypropyl methylcellulose having viscosity of from about 100 to about 100,000 cps and other excipients; compressing the granules into a tablet; wherein the tablet provides therapeutically effective plasma levels of gabapentin for a period of upto about 12 hours.

26. A process according [redacted]aim 1 wherein sustained release [redacted]et of gabapentin comprises granulating a mixture of a therapeutically effective amount of gabapentin or a pharmaceutically acceptable salt or hydrate thereof; about 5% to about 80% of rate controlling polymer i.e. hydroxypropylcellulose having viscosity of from about 7 to about 30,000 cps and other excipients with water or a binder solution; compressing the granules into a tablet; wherein the tablet provides therapeutically effective plasma levels of gabapentin for a period of upto about 12 hours.

27. A process for the preparation of sustained release dosage form of gabapentin substantially as described and illustrated by the examples herein.

Dated **27TH** day of **May, 2003.**

For Ranbaxy Laboratories Limited

(Sushil Kumar Patawari)
Company Secretary

ABSTRACT

The present invention relates to sustained release oral dosage forms of gabapentin, particularly a tablet and a process for the preparation thereof. The sustained release tablet comprises gabapentin or a pharmaceutically acceptable salt or hydrates thereof and at least one rate-controlling polymer wherein the tablet provides therapeutically effective plasma levels of gabapentin for a period of up to about 12 hours.